## SOX2 modulates levels of MITF in normal human melanocytes, and melanoma lines in vitro.

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**Public Summary:**
Melanocytes, the pigment cells of the skin, originate during development from neural crest cells, a transient, plutipotent and highly migratory population of cells. Genetic mutations in melanocytes may result in melanoma, one of the most malignant and invasive type of tumors whose its incidence has been increasing at an alarming high rate in recent years. MITF is a transcription factor playing critical roles in both melanocytes and melanoma cell biology. It controls the molecular machinery dedicated to the production of melanin pigments and, more importantly, according to its levels of expression it can promote malignant proliferation (low levels), differentiation (high levels) or cell death (no expression) of melanoma cells. The transcription factor SOX2 is a master regulator of embryonic stem cell and neural precursor cell biology. Recently, It has been suggested that SOX2 also plays a role in both melanocyte development and melanoma progression. In fact, It has been noted that this pluripotency factor is re-expressed in approximately 45% and 40% of, respectively, primary and metastatic melanomas. Furthermore, several studies suggest that SOX2 functions as an oncogene in this type of tumor. In this work we explored the connection between this two important regulators of melanocytes and melanoma biology. We found that SOX2 functions as a modulator of MITF expression. Endogenous levels of SOX2 are in fact required to sustain the expression of MITF in all the cell lines analyzed. Interestingly however, overexpression of SOX2 also reduces the levels of MITF expression in at least one of the melanoma lines analyzed, thus suggesting a non-linear type of regulation. Overall, our work suggest that SOX2 is able to modulate the expression of MITF which, in turn, might contribute to the oncogenic function of SOX2 in this type of cancer. In the light of our results, it is in fact tempting to speculate that the SOX2 positive cells present within a melanoma tumor might represent the cells with low expresssion of MITF, suggested to be the proliferating cells within the lesion.

**Scientific Abstract:**
Malignant melanoma is one of the most invasive and metastatic tumors, and its incidence has been increasing at a higher rate than other cancers in recent years. The melanocytes master regulator, microphthalmia-associated transcription factor (MITF), has been also implicated in melanoma development and progression. Notably, current understanding of MITF role in melanoma development suggests a complex regulation which requires fine tuning of MITF expression. The SRY (sex determining region)-box 2 (SOX2) gene encodes a transcription factor required for maintenance of the pluripotent state of human embryonic stem cells (hESCs). Several neural crest-derived cell types in the adult skin such as dermal papillae and some MITF-positive melanocytes express SOX2. Intriguingly, 50% of primary and metastatic melanomas express Sox2 and downregulation of SOX2 was shown to reduce melanoma growth in vivo. Here we have investigated, at a single cell level, SOX2 and MITF expression in normal human melanocytes and melanoma cell lines by means of immunocytochemistry and found that the two transcription factors are co-expressed. We also employed Lentiviruses encoding SOX2 and SOX2-shRNAs to modulated SOX2 levels and found that SOX2 regulates MITF expression in human melanocytes and melanoma cells. Endogenous levels of SOX2 are in fact required to sustain the expression of MITF in all the cell lines analyzed. Interestingly however, overexpression of SOX2 also reduces the levels of MITF expression in at least one of the melanoma lines analyzed, thus suggesting a non-linear type of regulation. Overall, our work suggest that SOX2 is able to modulate the expression of MITF which, in turn, might contribute to the oncogenic function of SOX2 in this type of cancer. In the light of our results, it is in fact tempting to speculate that the SOX2 positive cells present within a melanoma tumor might represent the cells with low but detectable expression of MITF, suggested to be the proliferating cells within the lesion.